REMARKS/ARGUMENTS

Claims 1, 2, and 4-30 were pending in this application, of which claims 1, 2, 4-9, 11, 15-18, and 29-30 were under consideration. Claim 1 has been amended to clarify the language of the claim. However, such amendments do not narrow the scope of the claims in any regard. Claim 1 has also been amended to clarify the scope of the markush group. It is submitted that no new matters enters by way of the present amendment.

Claims 10, 12-14, and 19-28 have been withdrawn from consideration pursuant to 37 CFR 1.142(b), as being drawn to a non-elected inventions or species, pending rejoinder upon allowance of linking product and generic claims.

Hence, claims 1 and 6-30 remain pending, of which claims 1, 6-9, 11, 15-18, and 29-30 are under consideration. Entry of the amendment and reconsideration of the subject application as amended is respectfully requested.

Allowable Subject Matter/Claim Objections

Claims 6-7 and 18 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitation of the base claim and any intervening claims. Applicants thank the Examiner for the indication of allowable subject matter. However, Applicants have not currently amended the dependent claims, as it is submitted that the present claim set is in condition for allowance.

Claim Rejections Under 35 U.S.C. § 112, second paragraph

Claim 1 stands rejected under 35 U.S.C. §112, second paragraph, as being indefinite for allegedly failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The claim is allegedly indefinite due to the recitation of the terms "at least two spatially separate position[s] on a cell bound or soluble target molecule" and "enters into interactions with [said] cell-bound or soluble target molecule". While not agree that the claim was indefinite as worded, the claim preamble has been amended to recite that the reagent enters into interactions with at least two spatially separated positions on CD30. The body of the claim

then further clarifies the nature of the interactions. However, such amendments do not narrow the scope of the claim in any regard.

As such, it is submitted that the claims comply with 35 U.S.C. §112, second paragraph, and withdrawal of this rejection is respectfully requested.

Claim Rejections Under 35 U.S.C. § 112, first paragraph - Written Description

Claims 1, 8, 9, 11, 15-16 and 29-30 stand rejected under 37 U.S.C. §112, first paragraph, as allegedly failing to comply with the written description requirement. This rejection is respectfully traversed for at least the reasons which follow.

The Examiner acknowledges that the antibody to the epitope CEPDY of CD30, produced by a cell DSM ACC 2548 meets the written description requirement. However, in support of the rejection, the Examiner alleges that the structural feature of the CEPDY binding molecule would be significantly different among an antibody, a T-cell receptor and other reagents, although they all could bind to a core sequence of CEPDY. The Examiner further asserts that one skilled in the art would know that the structure and sequence of an antibody to an epitope of amino acid sequence CEPDY is different from the structure of a T-Cell receptor or a hybrid scFv/sc TCR fragment, or any other reagent.

The purpose of the written description requirement is simply to ensure that the inventors had possession of the claimed subject matter, *i.e.*, to ensure that the inventors actually invented what is claimed. *See Gentry Gallery Inc. v. Berkline Corp.*, 134 F.3d 1473, 1479, 45 USPQ2d 1498, 1503 (Fed. Cir. 1998); *Lockwood v. American Airlines*, 107 F.3d 1565, 1572, 41 USPQ2d 1961, 1966 (Fed. Cir. 1997); *In re Alton*, 76 F.3d 1168, 1172, 37 USPQ2d 1578, 1581 (Fed. Cir. 1996). In accordance with this purpose, Applicants need not "describe," in the sense of Section 112, all things that are encompassed by the claims. To contend otherwise would contradict established jurisprudence, which teaches that a patent may be infringed by technology developed after a patent issues. *United States Steel Corp. v. Phillips Petroleum Co.*, v865 F.2d 1247, 1251, 9 USPQ2d 1461, 1464 (Fed. Cir. 1989).

A related and equally well-established principle of patent law is that claims "may be broader than the specific embodiment disclosed in a specification." *Ralston Purina Co. v.*

Far-mor-Co, 772 F.2d 1570, 1575, 227 USPQ 177, 179 (Fed. Cir. 1985) (*quoting In re Rasmussen*, 650 F.2d 1212, 1215, 211 USPQ 323, 326 (CCPA. 1981)). Thus, simply because the claims may also include reagents beyond those reduced to practice in the specification does not require that Applicants describe each and every one of these molecules by their sequence. Further, "a description as filed is presumed to be adequate, unless and until sufficient evidence or reasoning to the contrary has been presented by the examiner to rebut the presumption." *Federal Register* 66(4):1107, Written Description Guidelines (2001). In this regard, the Examiner is required to disclose "express findings of fact which support the lack of written description conclusion." *Id.*

Applicants have provided the structural attribute of the core sequence of the epitopes of the CD30 antigen to which the reagents bind. As such, again, Applicants have provided "structural feature[s] possessed by members of the [claimed] genus that distinguish[] them from others." *Regents of the University of California v. Eli Lilly and Co.*, 119 F.3d 1559, 43 USPQ2d 1398 (Fed. Cir. 1997). Further, applicants have provided extensive guidance concerning means for constructing the reagents of the inventions. As such, once the CEPDY epitopes of CD30 in two spatially separate positions and the basic design of the binding reagents described in the present specification were known, those skilled in the art would recognize that the inventors were in possession of the claim reagents of antibody fragments, chimerized antibodies, humanised antibodies, scFv fragments, TCR fragments, and hybrid scFV/scTCR fragments.

As stated in the Revised Interim Written Description Guideline Training Materials at page 60, "[c]onsidering the routine art-recognized method of making antibodies to fully characterized antigens, the well defined structural characteristics for the five classes of antibody, the functional characteristics of antibody binding, and the fact that the antibody technology is well developed and mature, one of skill in the art would have recognized that the spectrum of antibodies which bind to antigen X were implicitly disclosed as a result of the isolation of antigen X." In the present case, given that the CD30 antigen was isolated and characterized, and that the CEPDY epitopes in two spatially separated positions were identified at the structural feature of interest to binding, one of skill would have recognized that the spectrum of the well

characterized binding reagents were disclosed as a result of the isolation and characterization of the structural features of the epitope.

For at least these reasons, it is submitted that the claims comply with 35 U.S.C. §112, first paragraph, and withdrawal of this rejection is respectfully requested.

Claim Rejections Under 35 U.S.C. § 102

A. Lemke

Claims 1-2, 4-6, 15 and 29-30 stand rejected under 35 U.S.C. §102(b) as allegedly being anticipated by the cited portions of U.S. Patent No. 6,033,876 to Lemke, *et al.* (hereinafter "Lemke"). This rejection is respectfully traversed for at least the reasons which follow.

Again, the rejected claims generally relate to a reagent that enters into interactions with at least two spatially separated positions on CD30; the at least two spatially separated positions each comprise an eptiope having a core sequence CEPDY; and the reagent enters into interactions with each of the at least two spatially separated positions on CD30 *via* binding to the epitope with a core sequence CEPDY.

Whatever else Lemke does disclose, it does not disclose a reagent that interacts with at least two spatially separated positions on CD30 with core sequences CEPDY, much less a reagent selected from the group consisting of antibody fragments, chimerized antibodies, humanised antibodies, single chain (sc)Fv fragments, scT-cell receptor (TCR) fragments, and hybrid scFv/scTCR fragments with such characteristics.

In support of the rejection, the Examiner asserts that "[o]ne skilled in the art would know antigen binding fragment developed using a specific antigen, such as CD30, would include all the possible antigen binding fragments, which would likely interact with any possible epitope of the antigen comprising the CEDPY on CD30." *Office Action mailed December 19, 2005* at Page 5. Further, the Examiner alleges that "[s]ince the Applicants do not provide any evidence indicating the antibodies of Lemke et al., do no bind to the two spatial epitope, CEPDY, of CD30 [...], the antibodies of Lemke et al., still read on the claimed reagent." *Id.* Again, Applicants respectfully traverse.

It is again submitted that the burden does not properly shift to the applicant unless the Examiner has first established that the claims are "*reasonably* considered as possessing the allegedly inherent characteristics" of the prior art (*In re Best*, 195 USPQ 430, 433 (CCPA 1977), emphasis added). "Inherency ... may not be established by *probabilities or possibilities.*" *Mehl/Biophile v. Milgraum,* 52 USPQ2d 1303, 1305 (Fed. Cir. 1999) (emphasis added). "The mere fact that a certain thing *may* result from a given set of circumstances *is not sufficient* to establish inherency." *In re Rijckaert*, 28 USPQ2d 1955 (Fed. Cir. 1993) (emphasis added). Inherency cannot be based on probabilities or possibilities, particularly such remote ones. Therefore, it is submitted that the Examiner has not established a *prima facie* case of inherency to require rebuttal evidence from applicants.

In any event, the antibodies of Lemke are described as binding to the CD30 antigen, especially Ki-4. Col. 4, lines 20-22. Further, the exemplified antibody in Lemke is the "antibody Ki-4". Col. 5, lines 39-40. As illustrated and exemplified in Hansen *et al., The FASEB Journal*, 10.1096, published online March 19, 2004, the Ki-4 antibody disclosed by Lemke binds to an epitope that is different from the CEPDY epitope recognized by the reagents of the present invention. Hansen demonstrate that the Ki-4 antibody of Lemke bind a conformation epitope with a dominant binding region within CRD2 and 5 of CD30 (*see* page 7 or 17). As such, the data shows that the antibodies of Lemke do not in fact recognize the CEPDY epitope, as required by the claims.

For at least these reasons, this rejection is respectfully traversed, and withdrawal of this rejection is respectfully requested.

B. Francisco

Claims 1-5, 8-9 and 15-16 stand rejected under 37 U.S.C. §102(e) as being allegedly anticipated by the cited portions of U.S. Patent Publication No. 2004/0018194 to Francisco, *et al.* (hereinafter "Francisco"). This rejection is respectfully traversed for at least the reasons which follow.

Whatever else Francisco does disclose, it does not disclose a reagent that interacts with at least two spatially separated positions on CD30 with a core sequence CEPDY.

In support of the rejection, the Examiner again asserts that "[o]ne skilled in the art would know antigen binding fragment developed using a specific antigen, such as CD30, would include all the possible antigen binding fragments, which would likely interact with any possible epitope of the antigen comprising the CEDPY on CD30." *Office Action mailed December 19, 2005* at Page 5. Further, the Examiner alleges that "[s]ince the Applicants do not provide any evidence indicating the antibodies of Francisco et al., do no bind to the two spatial epitope, CEPDY, of CD30 [...], the antibodies of Francisco et al., still read on the claimed reagent." *Id.*

The antibody disclosed by Francisco appears to be a CD30 antibody having strong agonistic activity. By way of background, in TNF-receptors such as CD30, the intracellular signal is triggered by crosslinking of the receptor molecules. The agonistic activity is particularly strong if the antibody has two binding sites binds, and therefore crosslinks two different receptor molecules. The strong agonistic activity of the antibodies of Francisco are likely due to such crosslinking. In contrast, the reagents of the invention binding two spatially separated CEPDY epitopes located within the single receptor molecule only trigger a very weak intracellular CD30 receptor mediated signal. It therefore appears to be quite unlikely, if not impossible, that the antibody of Francisco recognizes two spatially separated CEPDY epitopes located within the same CD30 molecule, as required by the present claims.

As discussed above, inherency cannot be based on probabilities or possibilities. Given the great variability in antibodies elicited to a single target, it would be mere coincidence if the antibody of Francisco happened by chance to interact with two spatially separated positions on CD30, as well as bind to the core sequence CEPDY, as required by the independent claim. Therefore, it is submitted that the Examiner has not established a *prima facie* case of inherency to require rebuttal evidence from applicants.

For at least these reasons and the reasons discussed above with reference to Lemke, this rejection is respectfully traversed, and withdrawal of this rejection is respectfully requested.

Claim Rejections Under 35 U.S.C. § 103(a)

Claims 1, 8-9 and 11 stand rejected under 35 U.S.C. § 103(a) as being allegedly unpatentable over Lemke, in view of the cited portions of Deonarain, *et al.*, *Br. J. Cancer*, Vol. 70, p. 786-94 (1994) (hereinafter "Deonarian"). This rejection is respectfully traversed for at least the reasons which follow.

Initially, as discussed above, whatever else Lemke does disclose, it does not disclose a reagent that interacts with at least two spatially separated positions on CD30, or a reagent which binds an epitope with a core sequence CEPDY. The Ki-4 antibody of Lembke does not, in fact bind to an epitope having a core sequence CEPDY, but rather binds to a conformational epitope i within CRD2 and 5 of CD30. Absent an express teaching of interactions with at least two spatially separated positions on CD30 *via* binding to the epitope with a core sequence CEPDY, one of skill would not be lead to specifically design and/or obtain antibody fragments, chimerized antibodies, humanised antibodies, scFv fragments, scTCR fragments, or hybrid scFv/scTCR fragments with such specific characteristics.

The patentability of the presently claimed invention, as compared to the state of the art, is further evidenced by the unexpected ability of the claimed reagent to bind to at least two spatially separate positions on the target molecule. Due to this ability, the claimed reagent possesses a much higher probability that the target molecule does not completely lose its ability to be recognized by the regent in case a mutation occurs in the target molecule. In contrast, with binding compounds known from the state of the art, there is a high risk of this to happen. For example, if the mutation affects the binding site on the target molecule, either directly (*e.g.*, within the epitope) or indirectly (*e.g.*, by a confirmation change), this leads to a loss of the ability of the binding molecule to recognize the target site (*see, e.g.*, page 2, second paragraph of the original specification). As a result, *e.g.*, in the context of diagnostics, an incorrect negative result would be produced and subsequent therapy could fail completely. Because the presently claimed reagent enters into interaction with the target molecule in at least two positions, the loss of one of the binding sites, *e.g.*, by mutation, does not lead to complete loss of the binding since the reagent still reacts with a second binding site. This surprising property of the presently claimed invention results, *inter alia*, in a clearly increased reliability of diagnosis.

In addition, the presently claimed reagent surprisingly also produces an increased sensitivity in diagnosis and an increased effectiveness in therapy (*see, e.g.,* page 3, third paragraph of the original specification). The increased sensitivity stems, in part, from the fact that twice as much reagent can bind to a single cell compared to reagents known in the art. The increased amount of binding of the reagent in turn leads to a stronger detection signal of the sample to be analyzed. In the context of therapy, this surprising property is also very versatile since compared to binding molecules known in the art, due to a stronger binding to the target molecule, a larger quantity of reagent can be taken up by a target cell so that a correspondingly stronger therapeutic effect on the target cell may be elicited, *e.g.*, by activation of the complementary system or by incorporation of toxins or radioactive isotopes which can ultimately kill the target cell (*see, e.g.*, page 3, third paragraph of the original specification) resulting in a more effective therapy.

Finally, the particular surprising properties of a reagent encompassed by the amended claims have also been demonstrated in the Examples of the specification. Such reagents bind CD30 with high affinity (*see, e.g.*, page 15, second paragraph of the original specification), and are able to produce a strong antibody-dependent cytotoxicity (*see, e.g.*, page 15, last paragraph to page 16, first paragraph of the original specification).

Regardless of the unexpected properties of the claimed reagents, it is submitted that the Examiner has failed to establish a *prima facie* case of obviousness. Whatever else Lemke and Deonarain may disclose or suggest, neither reference alone or in combination suggests the desirability of a reagent capable of interacting with two spatially separated positions on CD30, as well as binding to the core sequence CEPDY.

Moreover, without agreeing that one of skill in the art would be motivated to combine the teaching of Deonarian and Lemke, even assuming *arguendo* such a combination, Deonarian does nothing to remedy the deficiencies of Lemke.

To establish a *prima facie* case of obviousness, the prior art reference (or references when combined) must teach or suggest all of the claim limitations. There must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference

teachings. The teaching or suggestion to make the claimed combination must be found in the prior art, and not be based on applicants' disclosure. *See M.P.E.P.* §§2143.01 and 2143.03.

Absent a teaching or suggestion, either in the references themselves or the knowledge of those skilled in the art, to modify the antibodies of Lemke to arrive at the presently claimed reagents, it is submitted that the cited references do not render the claimed invention obvious.

For at least these reasons, this rejection is traversed, and withdrawal of this rejection is respectfully requested.

CONCLUSION

In view of the foregoing, Applicants believe all claims now pending in this Application are in condition for allowance. The issuance of a formal Notice of Allowance at an early date is respectfully requested.

If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at 303-571-4000.

Respectfully submitted,

Milan M Vinnola

Milan M. Vinnola
Reg. No. 45,979

TOWNSEND and TOWNSEND and CREW LLP
Two Embarcadero Center, Eighth Floor
San Francisco, California 94111-3834
Tel: 303-571-4000
Fax: 415-576-0300

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